AR201-13629A

HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN
FOR
METHYL ISOPROPYL KETONE
(CAS NO.: 563-80-4)

PREPARED BY:

EASTMAN CHEMICAL COMPANY

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OVERVIEW

The Eastman Chemical Company hereby submit for review and public comment the test plan for methyl isopropyl ketone (MIPK; CAS NO.: 563-80-4) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of our company to use existing data on MIPK in conjunction with EPA-acceptable predictive computer models to adequately fulfill the Screening Information Data Set (SIDS) for the physicochemical, environmental fate, ecotoxicity test, and human health effects endpoints. We believe that in total these data are adequate to fulfill all the requirements of the HPV program without need for the conduct any new or additional tests.

Methyl isopropyl ketone is a water-white liquid that is manufactured to a high degree of purity. This ketone finds its primary uses in industrial applications where it is utilized as an intermediate in the synthesis of other chemicals and as an industrial solvent. It may also find some use as a solvent in coatings applications. Industrial work place exposure levels for this chemical have been established by the ACGIH, which set a TLV-TWA of 200 ppm (705 mg/m^3).

TEST PLAN SUMMARY

CAS No. 563-80-4	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA							
Melting Point	Y	-	-	Y	N	Y	N
Boiling Point	Y	-	-	Y	N	Y	N
Vapor Pressure	Y	-	-	Y	N	Y	N
Partition Coefficient	Y	-	-	Y	N	Y	N
Water Solubility	Y	-	-	Y	N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	-	-	Y	N	Y	N
Stability in Water	Y[1]	-	-	Y	N	Y	N
Biodegradation	Y	Y	-	-	Y	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	-	Y	-	N	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	-	Y	-	N	Y	N
Toxicity to Aquatic Plants	Y	Y	-	-	Y	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y	-	Y	-	Y	Y	N
Repeated Dose Toxicity	Y	-	Y	-	Y	Y	N
Genetic Toxicity – Mutation	Y	Y	-	-	Y	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	Y	-	-	Y	Y	N
Developmental Toxicity	Y	Y	-	-	Y	Y	N
Toxicity to Reproduction	Y	Y	-	-	Y	Y	N

1. A technical discussion has been provided.

TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT

A. Physicochemical

Melting point - A value for this endpoint was obtained using a computer estimation model.

Boiling Point - A value for this endpoint was obtained using a computer estimation model.

Vapor Pressure - A value for this endpoint was obtained using a computer estimation model.

Partition Coefficient - A value for this endpoint was obtained using a computer estimation model.

Water Solubility - A value for this endpoint was obtained using a computer estimation model.

Conclusion: All end points haven been satisfied by the utilization of data obtained from the various physical chemical data modeling programs within the EPIWIN suite (1). The results from the utilization of the models within this program have been noted by the Agency as acceptable in lieu of actual data or values identified from textbooks (2). No new testing is required.

B. Environmental Fate

Photodegradation - A value for this endpoint was obtained using a computer estimation model.

Stability in Water - A technical discussion describing the stability of ketones in water was provided.

Biodegradation - This endpoint was satisfied through data derived from a study that followed an established OECD test guideline (301-D) and was conducted under GLP assurances.

Fugacity - A value for this endpoint was obtained using the EQC Level III partitioning computer estimation model.

Conclusion: All endpoints have been satisfied using actual data or through the utilization of Agency-acceptable estimation models (2). A technical discussion was used to fulfill the endpoint assessing the stability of MIPK in water. In total, they are of sufficient quality to conclude that no additional testing is needed.

C. Ecotoxicity Data

Acute Toxicity to Fish - This endpoint is filled by data from a well-conducted study with acceptable methods.

Acute Toxicity to Aquatic Invertebrates - This endpoint is filled by data from a well-conducted study with acceptable methods.

Toxicity to Aquatic Plants - This endpoint is filled by data from an OECD TG-201 study conducted under GLP assurances.

Conclusion: All endpoints have been satisfied with data from well-conducted studies using acceptable methodologies. While the data from the fish and Daphnia studies were not conducted under GLP assurances, their results are of sufficient quality to conclude that no additional testing is needed.

D. Toxicological Data

Acute Toxicity - This endpoint is filled by data from studies conducted in rats that assessed the toxicity of MIPK following both oral and inhalation exposures. Although the studies did not follow standardized guideline protocols, they were conducted under GLP assurances. The quality of these studies was deemed as “reliable without restrictions”.

Repeat Dose Toxicity - This endpoint is filled by data from an inhalation study of 28-days duration. The protocol followed was comparable to that of an OECD-412 guideline and the study was conducted under GLP assurances. The quality of this study was deemed as "reliable without restrictions".

Genetic Toxicity Mutation - This endpoint is filled with a study that followed OECD guideline #471 and was conducted under GLP assurances. This study utilized *Salmonella typhimurium* (strains TA 98, 100, 1535, 1537, and 1538) and *Escherichia coli* (strain WP2*uvr*A). The quality of this study was deemed as "reliable without restrictions".

Aberration - This endpoint is filled with data from an *in vitro* study using Chinese hamster ovary (CHO) cells that followed OECD guideline #473 and was conducted under GLP assurances. The quality of this study was deemed as "reliable without restrictions".

Developmental Toxicity - This endpoint is filled by data from an inhalation exposure study in rats that followed OECD guideline #421 and was conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential. The quality of this study was deemed as "reliable without restrictions".

Reproductive Toxicity - This endpoint is filled by data from an inhalation exposure study in rats that followed OECD guideline #421 and was conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential. The quality of this study was deemed as "reliable without restrictions".

Conclusion: All endpoints have been satisfied with data from studies whose methods followed established OECD guidelines, or utilized methods that were very similar and scientifically appropriate. All studies were conducted under GLP assurances. In total they were all of sufficient quality to deem them as "reliable without restrictions" and to conclude that no additional testing is needed.

SIDS DATA SUMMARY

Data assessing the various physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility) for MIPK were all obtained from computer estimation models within the EPIWIN suite. These data indicate that MIPK is a liquid at room temperature with a relatively low vapor pressure. It has a low estimated octanol to water partition coefficient and accordingly is quite soluble in water despite being classified as "slight".

The assessment of the environmental fate endpoints (photodegradation, biodegradation, stability in water, and fugacity) was completed through the use of an actual study, acceptable estimation modeling programs, and a technical discussion. As a result of its solubility in water and relatively low volatility, fugacity estimations predict that MIPK will distribute primarily to soil and water. A technical discussion has been provided that indicates this ketone is not likely to under go hydrolysis. The available biodegradation data indicate MIPK is likely to be readily degraded in the environment. It primary use is in industrial applications environmental releases will primarily occur through evaporative emissions where MIPK is expected to degrade in the atmosphere at a moderate to slow rate.

The potential toxicity of MIPK to fish, Daphnia, and algae were determined through well-conducted studies. The results of these studies demonstrate fish and Daphnia are not sensitive species with both having a NOEC >100 mg/L. However, the NOEC of MIPK on algal growth was determined to be 14.8 mg/L. Based on these data MIPK would be classified as "harmful to aquatic organisms" according to the European Union's labeling directive but

would be classified in a "moderate concern level" according to the U.S. EPA's assessment criteria. The potential for exposure to aqueous environments is unlikely due to its primary uses in industrial applications. Furthermore, MIPK is noted as being readily biodegradable.

The potential to induce toxicity in mammalian species following acute oral and inhalation exposures is very low. The oral LD_{50} value in rats is 3,078 mg/kg, while data from an inhalation study in rats yielded an LC_{50} of 6,377 ppm (22,464 mg/m^3) following a 6-hour exposure. Data from a repeat inhalation exposure study in rats at levels of 750, 1,500, and 3,000 ppm (2,642, 5,284, and 10,569 mg/m^3) for a duration of 28-days indicated the material was well tolerated with minimal evidence of toxicity. No NOEL was established in this study as clinical signs of toxicity (narcosis and lethargy) were seen at all levels. However, they rapidly diminished after exposure cessation and the primary effect noted was a non-specific decrease in body weight at the highest two exposure levels. A possible cause of this decreased weight gain could have be a decrease in food consumption related to the time needed to recover from the exposure-induced depression. Furthermore, there was minimal evidence of any target organ toxicity based on a lack of changes in absolute organ weights and normal histological appearances (males showed evidence of hyaline droplets). Hyaline droplet formation seen in the kidneys of males is not relevant to humans. Results from mutagenicity and chromosomal aberration studies indicate this material is not genotoxic. Developmental and reproductive toxicity endpoints were assessed simultaneously through the conduct of a developmental/reproductive toxicity screening inhalation study in rats that followed OECD test guideline #421. Results from this study indicate MIPK is not likely to induce either type of effect. No NOAEL was determined for matemal effects as signs of toxicity (reductions in general activity levels) were noted in all treated groups during the inhalation exposures. In addition, lower mean body weight gain and feed utilization was noted in all three treatment groups. The NOAEL for fetal effects was 1 mg/L (1,000 mg/m^3).

In conclusion, an adequate assessment and summarization of all the Screening Information Data Set (SIDS) endpoints has been completed to satisfy the requirements of the HPV program without need for the conduct of any new or additional tests. This data set consists of results from studies conducted on MIPK that either followed established protocols under GLP assurances or scientifically acceptable procedures to assess the various endpoints. Where appropriate, some endpoints have been fulfilled through the utilization of data from modeling programs accepted by the EPA. The summarized data indicate that this chemical, when used appropriately, should constitute a low risk to both workers and the general population.

EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general US EPA guidance (3) and the systematic approach described by Klimisch *et al.* (4). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation (5). The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

(1) Reliable without Restriction: Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

(2) Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

(3) Not Reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

(4) Not Assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

REFERENCES

1. EPIWIN, Version 3.01, Syracuse Research Corporation, Syracuse, New York.

2. US EPA. (1999). The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.

3. USEPA (1998). 3.4 Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.

4. Klimisch, H.-J., Andreae, M., and Tillmann, U. (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. *Regul. Toxicol. Pharmacol.* 25:1-5.

5. USEPA. 1999. Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.